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November 12, 2004

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Scientific Considerations Related to Developing "Follow-On" Protein Products (Docket No. 2004N-0355)

Dear Sir or Madam:

Pfizer Inc respectfully submits the attached comments in response to the Food and Drug Administration's notice of a Public Workshop on scientific considerations related to developing "follow-on" protein products.

Please do not hesitate to contact us if you have any questions regarding this submission.

Sincerely,

Fred

Encl.

2004N-0355 C 6

BEFORE THE FOOD AND DRUG ADMINISTRATION

Public Workshop Regarding Scientific Considerations Related to Developing "Follow-on" Protein Products [69 Fed. Reg. 50386 (Aug. 16, 2004)]	)	**Docket No. 2004N-0355**

Comments of Pfizer Inc.

November 12, 2004

COMMENTS ON SCIENTIFIC CONSIDERATIONS RELATED TO DEVELOPING "FOLLOW-ON" PROTEIN PRODUCTS

Pfizer Inc. ("Pfizer") respectfully submits these comments in response to the Food and Drug Administration's ("FDA's") notice of a public workshop regarding scientific considerations related to developing "follow-on" protein products (hereinafter referred to as "second-generation protein products").[1] Pfizer discovers, develops, manufactures, and markets leading prescription medicines, including innovative biologics, in more than 150 countries. Accordingly, Pfizer has a significant interest in FDA's development of a draft guidance document that addresses whether it is appropriate to develop abbreviated regulatory approval requirements for second-generation protein products. Pfizer applauds FDA for calling the scientific community together to discuss the issues associated with second-generation products, and appreciates the opportunity to participate in this important debate.

I. Executive Summary

Generally, second-generation protein products are significantly more scientifically complex than generic versions of chemically synthesized drug products. They are more complex because they involve live organisms in their production, have greater molecular weight and structural complexity, may involve multiple unique chemical entities within a single protein product, and may undergo complex post-translational modifications (*e.g.*, the addition of carbohydrates).

Protein products are particularly complex, variable, and fragile, and therefore, are quite susceptible to carry through of impurities and unintentional modifications during the manufacturing process, which can have material effects on safety and efficacy. Given that second-generation protein products will be derived from different organisms or starting materials, and will have different manufacturing processes, and containers and closures than their innovator predecessors, they are unique products that must be held to the same safety and efficacy standards as the innovator products. It is imperative that FDA develop a regulatory approach that permits such protein products to reach patients only if they have proven safety and efficacy profiles.

That being said, Pfizer believes that FDA should consider the feasibility of an abbreviated regulatory pathway for certain second-generation protein products. It is conceivable that less extensive preclinical and clinical testing could be defined in certain instances to demonstrate that a second-generation protein product is safe and efficacious for patients. Notably, however, FDA would have to take significant precautions, including a determination, on a case-by-case basis, as to whether the abbreviated approval process is appropriate. The regulatory process would likely be iterative, with

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[1] 69 Fed. Reg. 50386 (Aug. 16, 2004). Please note that Pfizer has addressed many of the scientific and legal issues associated with second-generation protein products in its *Citizen Petition Requesting FDA Rejection of Omnitrope*™ (Docket No. 2004P-0231 (May 13, 2004)). The contents of that Citizen Petition docket are hereby incorporated by reference.

With regard to nomenclature, for the reasons discussed in Section II(F) herein, Pfizer believes that the FDA's proposed distinction between "follow-on proteins" and "second generation protein products" is misleading and artificial. Thus, Pfizer recommends that FDA refer to all products that meet its current definitions of "follow-on proteins" and "second generation protein products" as "second-generation protein products." Accordingly, these comments refer to these types of protein products as "second-generation protein products" throughout.

preclinical and clinical studies required and designed based on data from earlier studies. In addition, robust phase IV post-marketing studies would be required to support any abbreviated regulatory process and protect patient safety. In summary, Pfizer strongly believes both preclinical and clinical data would be required, even in an abbreviated regulatory approval process, to confirm the safety and efficacy of a second-generation protein product.

In developing an approval process for second-generation protein products, FDA should bear in mind the following:

(1) **The manufacturing process significantly defines protein products** – Given the complexity, variability, and fragility of protein products, the final product's attributes are largely dependent on the organism or starting material specifications and all of the manufacturing processes. Because the specifications and processes are generally proprietary, second-generation protein products will be different from their predecessors. Therefore, for those products, preclinical and clinical studies are essential to validate the new specifications and manufacturing processes.

(2) **It is not possible to fully characterize protein products solely with analytical tests, and even the best analytical tests are insufficient to demonstrate safety and efficacy** – Current analytical technologies are not definitive for characterizing protein products. Even when specifically tailored to such a protein and the manufacturing processes at issue, many analytical tests are limited in their ability to detect minor structural changes or impurities and in their ability to measure all of the parameters that may have a bearing on safety and/or efficacy. Accordingly, only clinical studies, appropriately powered to examine sufficient numbers of patients, can establish the safety and efficacy of protein products.

(3) **Immunogenicity studies must be mandatory for second-generation protein products** – Given the complexity, variability, and fragility of such protein products, and their large molecular weight, undetectable changes in protein products could affect efficacy or trigger an immunogenic response, causing the body to attack healthy tissue. Accordingly, determining immunogenicity for second-generation protein products will typically require complete evaluation and study, including clinical studies and post-marketing surveillance.

(4) **Preclinical and clinical studies are necessary to establish the safety and efficacy of most second-generation protein products** – Because second-generation protein products are subject to different manufacturing processes than their predecessors, they are unique products that in the vast majority of cases must be held to the same testing requirements as the innovator product to ensure patient safety. Preclinical and clinical trials are essential given that: (1) even slight manufacturing differences can affect safety and/or efficacy; (2) observed immune response(s) to product or process-related impurities can vary widely from patient to patient; and (3) current analytical technology cannot adequately characterize protein products to predict safety and efficacy.

(5) **Bioassays are inadequate tools for comparing innovator products with most second-generation protein products** – Bioassays lack the precision and reproducibility necessary to compare the potency, safety, and efficacy of such products. Moreover, bioassays typically cannot predict the effect of structural changes and/or impurities on the safety and efficacy of such products. Finally, there is no way of knowing whether bioassays for such products

have measured all of the relevant parameters concerning safety and efficacy, without the confirmation of clinical studies. In fact, with complex biologicals, such as low molecular weight heparins ("LMWHs"), the literature clearly indicates that the well-known coagulation parameters used to characterize the anti-thrombotic properties of these large biologicals have no value in evaluating the anti-proliferative activity[2] or the anti-tumor potential of these agents.

(6) **Products that fall within FDA's current definition of "follow-on proteins" and "second generation protein products" should all be referred to as "second-generation protein products," and in most cases should be identified by distinct non-proprietary names** – The FDA's proposed distinction between "follow-on proteins" (*i.e.*, products that are likely to be different from their innovator predecessors) and "second generation protein products" (*i.e.*, products that are different than their predecessors, by definition) is misleading and somewhat artificial. Given the limited ability of analytical technologies to prove the safety and efficacy of most protein products, preclinical and clinical studies are typically critical to show safety and efficacy, regardless of whether the differences between the new products and the predecessors are known, unknown, or merely potential. In addition, the absence of similarity between innovator protein products and most second-generation products should be reflected clearly in labeling, and in the nonproprietary names chosen for those products. Among other constraints, in most cases second-generation versions of protein products should not be permitted to declare the same United States Adopted Name ("USAN") as the innovator product.

II. Pfizer's Responses to the Specific Questions Posed by FDA's Notice of Public Workshop

A. Manufacturing Issues

1. The Manufacturing Process Significantly Defines Most Protein Products

In its notice regarding the public workshop, FDA asks: "What aspects of the manufacturing process determine the characteristics of a protein product whether produced through biotechnology or derived from natural sources?"[3]

As noted, protein products are more complex than traditional chemically synthesized drug products due to higher molecular weights and more complex chemical structures. Such protein products, generally, are produced in living cells, and therefore, are more variable than traditional synthesized drug products. This complexity and variability make protein products more susceptible to impurities and unintentional modifications during the manufacturing process.

Accordingly, to protect against protein alterations and associated safety and efficacy issues, it is essential that the following three major parts of the manufacturing process are adequately controlled and validated for protein products: (1) the starting materials or the organism (*e.g.*, DNA sequence,

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[2] H.G. Garg, *et al.*, *Structural determinants of antiproliferative activity of heparin on pulmonary artery smooth muscle cells*, 279(5) Am. J. Physiol. Lung Cell Mol. Physiol. L779 (2000).

[3] 69 Fed. Reg. at 50387.

plasmid construct, the organism and strain, and the Master Cell Bank ("MCB"), and the working cell bank derived from the MCB, which are proprietary to the company and specific to the product), (2) the procedures for preparing the drug substance (*e.g.*, fermentation, harvesting, selectivity and specificity of isolation/purification steps), and (3) the procedures for preparing the final drug product (*e.g.*, formulation (including excipients and preservatives), filling, lyophilization and container/closure).

Notably, consistent with the *FDA Guidance Concerning Demonstrating Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* ("*FDA Comparability Guidance*")[4] – which addresses manufacturing changes to products *within* the same company – when innovator companies make significant changes to their manufacturing processes, but still use the same MCB, they ensure that the resulting protein product is equally as safe and efficacious as the original, through a combination of analytical, preclinical, and clinical studies, as appropriate. Demonstrating similarity between an original and a second-generation protein product is substantially more difficult because starting material specifications and manufacturing processes remain proprietary to innovators.

Moreover, second-generation product manufacturers simply do not have the MCB, nor the product development experience of the innovators (*e.g.*, in-process testing, typical in process elution profiles and in process samples, toxicology studies, *in vivo* pharmacokinetic and pharmacodynamic studies, reagents, and reference standards). Accordingly, with second-generation protein products, slight alterations of the protein product due to the manufacturing differences, which could affect safety and efficacy, are more likely to occur and go undetected. Thus, for the vast majority of second-generation protein products, validation of the manufacturing process with full preclinical and clinical testing would be critical to ensure the safety and efficacy of the final product.

a. Starting Material[5]

The starting material, or the initial organism, selected in the manufacturing process is essential to the final integrity of the protein product, and is defined by the MCB. From this MCB, well-defined and validated working cell banks are made, which are used to start each new fermentation step. For example, epoetin alfa products that are approved in the U.S. and Europe are qualitatively and quantitatively different from those in other parts of the world. The difference is the organism – although they are all presumably erythropoetins made in mammalian cell cultures, the products contain different glycosylated species.[6]

As another example, Fragmin®, a low molecular weight heparin drug product ("LMWH"), like other LMWHs, is exceedingly dependent upon the quality and attributes of the starting material. The starting material, pharmaceutical grade heparin, is a complex biological mixture that is highly variable and composed primarily of mixtures of polydisperse glycosaminoglycans ('GAGs"). The

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[4] *FDA Guidance Concerning Demonstrating Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* (Apr. 1996).

[5] Throughout the remainder of these comments, we will refer to "the starting material or organism" to indicate that whether the protein product is produced through biotechnology or through more traditional pharmaceutical methods, the respective initial materials and the manufacturing process are to be considered.

[6] *See* H. Schellekens, 3 European Journal of Hospital Pharmacy Science 43 (2004).

molecular weight of the individual chains varies from 5,000 to over 40,000 Daltons and displays significant sequence heterogeneity. Given this variability, innovator companies, such as Pfizer, have developed strict, proprietary starting material specifications.

The quality of the starting materials is important because impurities can result from the product itself, such as fragments or aggregates of the protein or chemical modifications of the product – just as easily as they can result from outside sources. Indeed, with Fragmin®, Pfizer has developed proprietary processes to remove specific contaminants from the starting material to ensure a safe and efficacious final product. Subsequent published work has also shown a specific structure activity relationship between the type and degree of sulfation of certain chemical bonds in LMWHs and the efficacy of the LMWH in causing vascular proliferation.[7]

Moreover, for most protein products, the attributes of the starting material affect which in-process controls are necessary further down the line. For Fragmin®, Pfizer adjusts subsequent process steps based on the potency and other variables of the starting product. The same applies to the manufacturing process for Genotropin®, a recombinant human growth hormone ("rhGH"). Without strict adherence to proprietary starting material specifications and in-process controls that have been validated in clinical studies, there would be no way to ensure that protein products, such as Fragmin®, are safe and efficacious. Although a monograph standard for the active ingredient in Fragmin® (dalteparin sodium) has been established in Europe, and is currently being developed in the U.S., the monographs do not provide methods to fully characterize LMWHs. Therefore, any results based on monograph methods are not predictive of safety and efficacy.

b. Manufacturing Processes – The Drug Substance and the Final Drug Product

The manufacturing processes for both preparing the active protein and the finished product significantly define protein products. Pfizer has experienced this first-hand in manufacturing Genotropin®, an rhGH. With respect to Genotropin®, Pfizer discovered that there was a single disulfide bond that had been modified to a trisulfide in some of the molecules of rhGH product. Although it was difficult to determine the cause, Pfizer eventually determined that the structural change resulted from a trisulfide bond that was formed during the harvesting process used to prepare the drug substance. Because Pfizer had identified the impurity, the company was able to remove rhGH molecules containing the trisulfide bond during the isolation and purification process.

Manufacturing processes are also important in preparing the final drug product – even in the later stages, such as filling and packaging. In manufacturing Somatonorm®, for example, it was discovered that a polymer formed unexpectedly due to the geometry of a new stopper, leading to considerably shorter drying time needed in the lyophilizer.

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[7] *See* H.G. Garg, *et al.*, *Sulfation patterns in heparin and heparin sulfate: effects on the proliferation of bovine pulmonary artery smooth muscle cells*, 1639(3) Biochem. Biophy. Acta. 225 (2003); H.G. Garg, *et al.*, *Structural determinants of antiproliferative activity of heparin on pulmonary artery smooth muscle cells*, 279(5) Am. J. Physiol. Lung Cell Mol. Physiol. L779 (2000); H.G. Garg, *et al.*, *Antiproliferative role of 3-O-sulfate glucosamine in heparin on cultured pulmonary artery smooth muscle cells*, Biochem. Biophys. Res. Commun. 468 (1996).

Notably, these slight changes in the manufacturing processes can have a significant impact on safety and/or efficacy. For example, in 2002, Johnson & Johnson made a change in excipients in the finished Eprex® product, which contains a hormone used to treat certain types of anemia. The new product, in some patients, caused antibody-mediated pure red cell aplasia, which can be treated only with chronic blood transfusions.

In that case, the new product (*i.e.*, the product resulting from the change in excipient) did not display any significant analytical differences from the original product. However, during the latter part of the shelf-life of the new product, an impurity leached into the product from the closure stopper in some, but not all, of the containers of Eprex®. This post-production impurity likely served as an adjuvant in triggering the severe immunogenic response.

2. Assessing Similarity Between Products

In its Federal Register notice, FDA asks: "What parts of the manufacturing process should the agency focus on when assessing the similarity between products?"[8]

For protein products produced by recombinant techniques, Pfizer believes that FDA should focus on all parts of the manufacturing process, particularly: (1) plasmid construction, (2) host cell, (3) strain of host cell, (4) fermentation and ingredients, (5) harvesting procedures, (6) isolation and purification steps, (7) hold steps for intermediates, (8) procedures and handling during formulation and lyophilization steps, and (9) containers and closures. It is important to focus on all aspects of manufacturing because each aspect of the process can significantly define protein products. Different issues can arise at any stage in the manufacturing process, which can significantly alter the safety and/or efficacy of a biologic. As demonstrated by the examples above: (1) starting materials, such as those used for LMWH, can introduce impurities; (2) the harvesting process, such as the process used for Genotropin®, can introduce impurities; and (3) even container considerations, such as bottle stopper changes or geometry in the cases of Somatonorm® and Eprex®, can alter the final protein product's clinical safety and efficacy.

If companies do not focus on all aspects of manufacturing for such products, they may misidentify product anomalies that arise, and fail to rectify potential safety and efficacy issues. For example, in manufacturing Groliberin®, which is no longer marketed, Pfizer initially thought that we had identified the cause of an unexpected product alteration – a polymer formed during harsh lyophilization. However, the change was actually due to pthalate, a plastics softener, leaching from the tubing used in the filling equipment.

B. Characterization

1. The Usefulness of Current and Future Analytical Technology in Characterizing Protein Products

In its Federal Register notice, FDA asks: (1) "What is the capability of current analytical technology to adequately characterize protein products?"[9] *and (2) "Are there new technologies that hold promise for helping to characterize proteins?"*[10]

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[8] 69 Fed. Reg. at 50387

Analytical and characterization technology have long been used to ensure the consistency, quality, safety, and efficacy of chemically synthesized drug products. However, these same physical and chemical technologies are generally insufficient to fully characterize most protein products. As noted, characterization of these protein products is much more complex scientifically than characterization of chemically synthesized drug products. For example, such protein products involve live organisms in their production, have greater molecular weight and structural complexity, and are easily modified by the addition of carbohydrates. Degradation can also occur in inappropriate conditions. Moreover, protein structures often lack uniformity and may involve multiple chains (*e.g.*, insulin and immunoglobins). Accordingly, although small molecule, chemically synthesized drugs can be analyzed through straightforward chemical tests without full knowledge of the original manufacturing process because they contain fairly simple structures, the tests are less useful for most protein products, which are significantly more difficult to characterize.

In addition, the final composition of protein products is often unintentionally affected by the introduction of miniscule levels of impurities introduced via the starting material or the manufacturing processes. In some instances, the level of impurities introduced may be so low that they cannot be detected by current physical and chemical tests. However, because these protein products are exceedingly sensitive to their physical and chemical surroundings and can be easily modified, the impurities may adversely impact the efficacy or safety of the final product.

Accordingly, Pfizer believes that current analytical technologies are not sufficiently sensitive or robust to show sameness in characterizing protein products. Proprietary assays and reagents must be developed concurrently with the manufacturing process in order to measure appropriate product and host cell-related impurities as well, as container-derived contaminants. In addition, in the vast majority of cases, the entire manufacturing process for these protein products must be validated by preclinical and clinical tests that establish the safety and efficacy of the final product.

2. Relevant Factors When Assessing the Similarity of Different Proteins

In its Federal Register notice, FDA asks: "What factors, including quality attributes, impurity profiles, and changes in the manufacturing process, should be considered when assessing the similarity of different protein products?"[11]

Pfizer believes that the differences in the manufacturing process, impurity profiles, and quality attributes should all be considered when assessing the similarity of different protein products. The nature of these protein products, and their safety and efficacy, is inextricably linked to the starting materials and processes used to make the products. Moreover, current analytical tests are often limited in their ability to detect slight differences.

As previously mentioned, subtle changes in the manufacturing process or minor differences in the organism or starting materials can result in unintended and even undetected changes in different

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[9] *Id.* at 50387.

[10] *Id.* at 50388.

[11] *Id.*

batches of protein product produced by the same manufacturer. Thus, differences in the starting material or cell line, manufacturing processes, formulation, and the types of containers and closures used by a different manufacturer for a second-generation protein product could substantially affect the final product. In particular, minor differences in the starting materials and manufacturing processes can introduce impurities that are undetectable by current technologies. Given that changes to protein products can result in an ineffective product or trigger an immunogenic response, second-generation protein product manufacturers must be required to develop very specific and sensitive assays to test these products throughout the manufacturing processes.

Finally, as noted, even analytical tests that are tailored to individual manufacturing processes are insufficient to guarantee the safety and efficacy of second-generation protein products. Ultimately, preclinical and clinical studies – and for most protein products a full complement of such studies – will be critical to protecting public health.

3. Predictive Value of Analytical Studies

In its Federal Register notice, FDA asks: "Is it possible to accurately predict safety and efficacy from analytical studies?"[12]

In light of current technological limitations and the complex nature of most protein products, it is not possible to accurately predict safety and efficacy from analytical studies. Current technologies cannot establish pharmaceutical or therapeutic equivalence between such innovator and second-generation protein products. Experience shows that analytical testing does not reveal how these protein products will behave in the human body. Although abbreviating certain requirements may be appropriate in limited circumstances, clinical trials are the only way to characterize the clinical properties of second-generation protein products and accurately predict their safety and efficacy.

Pfizer's experience in developing Somatonorm® and Fragmin® underscores the limitations of current analytical technologies in adequately characterizing protein products, and predicting safety and efficacy. With Somatonorm®, a brand of rhGH, Pfizer discovered that the addition of the amino terminal methionine altered the immunogenicity of the protein, resulting in antibodies that could neutralize the action of growth hormone and slow down the rate of growth.[13]

Available analytical technologies, however, are limited in their sensitivity and specificity, and therefore, are unlikely to be able to detect such errors or mutations. It is doubtful that *in vitro* bioassays and comparable assays are sensitive enough to detect abnormal activity in rhGH products because mutations are present at a low level. Furthermore, it is not possible to predict the potential for a particular form of rhGH to trigger antibody formation because the mechanisms of antibody formation and the factors affecting this process are unknown.

Similarly, in developing Fragmin®, Pfizer discovered that available physio-chemical tests and markers for characterizing LMWHs cannot ensure the safety and effectiveness of such products.

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[12] *Id.*

[13] *See* S.L. Kaplan *et al.*, *Clinical Studies With Recombinant-DNA-Derived Methionyl Human Growth Hormone in Growth Hormone Deficient Children*, 1(8482) Lancet 697 (1986).

For example, errors in the length and spacing of the negatively charged sulfate groups of the oligosaccharide chains of LMWH, can cause Heparin-Induced Thrombocytopenia ("HIT"), an immunogenic disorder that can result in life-threatening consequences. Yet, there are no available analytical methods to precisely measure chain lengths and sulfation patterns. Recent studies have shown that "microheterogeneity," – *i.e.*, differences in chemical substitution and structure below the detection level of available technology – may be responsible for differences in functional properties of various LMWHs.[14]

Accordingly, without clinical studies to validate manufacturing practices, there is no way to determine whether products in either of these classes – rhGHs and LMWHs – are safe and efficacious.

C. Immunogenicity

1. Importance of Evaluating Immunogenicity

In its Federal Register notice, FDA asks: "How, and to what extent, should immunogenicity be evaluated for a "follow-on" protein product?"[15]

a. Immunogenicity Testing Should Be Mandatory for All Second-Generation Protein Products

Pfizer believes that it should be mandatory for manufacturers of each second-generation protein product to evaluate immunogenicity via clinical studies. Mandatory immunogenicity evaluations are particularly important for these products because they are likely to have different manufacturing processes, formulations, and containers/closures than their innovator predecessors.

Immunogenicity is critical in evaluating protein products. Unlike the small molecular structures of chemically synthesized drugs, the molecular structures of protein products are large enough to be recognized by the immune system. Even undetectable changes in protein products caused by changes in the manufacturing process or impurities could trigger an immunogenic response, causing the body to attack healthy tissue. Immunogenicity may also impact efficacy and the required dosing level of a product.

Immunogenicity can have dire health consequences. As noted above, Johnson & Johnson's alteration of the excipient for Eprex®, caused, in some patients, antibody-mediated pure red cell aplasia – a severe immunogenic response that requires chronic blood transfusions. Notably, this immunogenic response occurred despite the fact that the differences between the original product and the new product were undetected by the available range of analytical technologies.

In addition, studies have also shown that different protein products in the same category may be more or less conducive to the formation of antibodies that can affect the efficacy of a product. For

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[14] *See, e.g.*, H.G. Garg, *et al.*, *Sulfation patterns in heparin and heparin sulfate: effects on the proliferation of bovine pulmonary artery smooth muscle cells*, 1639(3) Biochem. Biophy. Acta. 225 (2003).

[15] 69 Fed. Reg. at 50388.

example, one study reported that two different *E. coli*-derived recombinant Granulocyte-Macrophage Colony-Stimulating Factor ("GM-CSF") products created different effects in colorectal patients. Of 20 patients treated with the first product, 19 developed anti-GM-CSF antibodies. In 9 of those patients, the antibodies neutralized the efficacy of the GM-CSF *in vitro*. However, of the 38 patients who received the second product, only 28 developed antibodies, and none of those antibodies neutralized the effect of the treatment.[16]

Product and process-related degradants, or host cell contaminants, can be immunogenic or become immunogenic by adjuvant action. Either way, immunogenicity is difficult to predict. For example, the manufacturers of generic rhGH, Omnitrope®, despite using technology that had been reliable for 20 years, found that a single batch of Omnitrope® was immunogenic due to host cell contaminants, which were not detected by current assay methods. Somatonorm® also suffered from immunogenicity that was linked to host cell contaminants. In that case, contamination that could not be identified created an adjuvant affect. A clinical study, however, revealed that there was a linear correlation between the amount of anti-*E. coli* (host cell protein ("HCP")) and anti-human growth hormone, proving that there was an *E. coli* contaminant. Removal of HCP reduced the antibody formation to very low levels.

b. Methods of Immunogenicity Evaluation

Pfizer believes that immunogenicity for most protein products should be evaluated by the following methods: (1) phase III clinical trials with *more than one* production scale lot, and (2) phase IV clinical trials, or post-marketing surveillance. Notably, while preclinical testing can give an indication of potential immunogenicity for such products, in the end the only appropriate testing is human testing. The absence of immunogenicity in animal testing does not guarantee its absence in humans. Moreover, as demonstrated by the GM-CSF study, different patients have different antibody responses to the same proteins, and therefore, only clinical testing can demonstrate the safety and efficacy of a protein product. Similarly, in the case of Somatonorm®, there was a difference between patient category and antibody response – *i.e.*, patients who had previously been treated with pituitary derived growth hormone did not respond to the therapy with antibodies, whereas naïve patients did. This finding was unexpected and demonstrates that second-generation protein products need to be tested in the whole range of patient groups and categories.

Finally, the importance of conducting phase III trials with more than one production scale lot is underscored, again, by the experience with Omnitrope® - where the one production batch that was used in the trial was contaminated with HCP, thereby causing antibody formation. Accordingly, performing clinical immunogenicity studies on more than one batch of second-generation protein products is typically essential.

2. Comparative Immunogenicity Studies

In its Federal Register notice, FDA asks: "Under what circumstances should comparative immunogenicity studies be conducted?"[17]

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[16] *See* M. Wadhwa *et al., Immunogenicity of Granulocyte-Macrophage Colony-Stimulating Factor (GMF-CSF) Products in Patients Undergoing Combination Therapy with GM-CSF*, 5 Clinical Cancer Research 1353 (1999).

[17] 69 Fed. Reg. at 50388.

As noted, Pfizer believes that immunogenicity studies should be mandatory for second-generation protein products. At a minimum, manufacturers should conduct a study comparing the immunogenicity and safety of a second-generation protein product and the innovator for one year. This comparative immunogenicity study should be followed with a tailored phase IV monitoring strategy to continue to track safety issues.

D. Preclinical and Clinical

In its Federal Register notice, the FDA asks: "When and how would it be appropriate to streamline or eliminate certain animal or human studies during development of a "follow-on" protein product?"[18]

Pfizer believes that it is inappropriate to streamline or eliminate certain animal or human studies during the development of most second-generation protein products. In fact, human studies should be mandatory. As noted in previous discussions, second-generation proteins are unique products that must be held to the same standards of safety and efficacy as the innovator. Preclinical and clinical trials are essential to establish safety and efficacy given that: (1) slight manufacturing changes can affect efficacy and/or safety; (2) different patients have different antibody responses to the same proteins; and (3) current analytical technology cannot adequately characterize protein products.

Pfizer's development experiences with Somatonorm® (rhGH) and Fragmin® (LMWH) underscore the importance of clinical trials. As noted, new versions of rhGH cannot be adequately characterized by physical and chemical tests because molecular variants and other impurities may be present at levels below detection. Moreover, bioassays of rhGH cannot replace clinical testing because they cannot predict clinical efficacy.

In addition, the alteration of chain length and charge density of certain chains in LMWH can lead to abnormal protein interactions, which can result in unintended clinical outcomes, like HIT (an immunogenic disorder that can result in life-threatening consequences). The clinical effects of structural changes (induced by a new manufacturing process) cannot be predicted given the complexity of LMWH molecules, the many LMWH-protein interactions in the body, and the lack of knowledge regarding LMWH's structure-activity relationships. Yet, clinical trials have demonstrated that slight changes in LMWHs may have dramatic effects on morbidity and mortality. Accordingly, proper characterization through clinical trials is necessary to protect patients from adverse events, especially given the increasingly common use of LMWHs in outpatient settings without clinician oversight.

Given the complexity of many protein products, such as rhGH and LMWH, and that small differences between protein products may greatly affect therapeutic value, it is simply unethical to subject patients to any incremental risk when safe and efficacious products are available. Although the incremental abbreviation of requirements may be appropriate in certain circumstances, approving inadequately characterized second-generation protein products without clinical trials would present an unreasonable risk given that safe and tested products are on the market.

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[18] *Id.*

E. Potency and Surrogates for Efficacy and Safety

In its Federal Register notice, FDA asks: (1) "What factors should be considered regarding bioactivity and potency assays used for comparing two products?" and (2) "What is the role of in vitro and in vivo assays for use as surrogates in establishing safety and efficacy?"[19] *Read together, these questions essentially ask whether bioassays are useful in comparing two products, and whether they are useful as surrogates in establishing safety and efficacy.*

As an initial matter, bioassays have high intra- and inter-assay variability. Therefore, they lack the precision and reproducibility necessary to compare protein products. For instance, potency assays for Genotropin®, Pfizer's rhGH, can detect a loss of potency only when the loss exceeds 50%. Thus, for rhGH, there may be no way to detect that a second-generation protein product is 45%, or 30% less potent than an innovator product. Yet, such a substantial reduction in potency for rhGH would be highly relevant to the product's efficacy for a patient. Indeed, even a minor loss of bioactivity in many protein products can result in poor long-term clinical effects, particularly with chronic treatment.

In addition, there are currently no predictive, validated surrogates or markers, such as bioassays, capable of fully establishing safety and efficacy for protein products in lieu of clinical trials. As demonstrated by the Genotropin® example, bioassays, regardless of whether they are *in vivo* or *in vitro*, are not always accurate enough to identify clinically relevant differences in efficacy. Moreover, assays may not be sensitive enough to detect contaminants that materially affect safety. Indeed, bioassays are often performed in a non-primate species or in modified cell lines, and can only detect short-term effects. Further, most proteins have many metabolic, physiologic, and anatomical effects. No single assay can measure all of these activities in proteins, and even multiple assays are unlikely to catch all of the differences between an innovator and second-generation product.

Even if a predictive bioassay for a protein product could be developed, properly powered human trials would be required to validate that bioassay as a regulatory surrogate. Each successive second-generation protein product would have to provide its own validation of the surrogate, with few exceptions, through a demonstration of clinical efficacy and safety in phase III studies. As noted, surrogates are commonly limited in the range of properties that they can detect, which are important to characterizing a particular product. Therefore, more than one surrogate typically will be required for full characterization. "Full characterization" implies that there is an awareness of all of the properties important in characterizing the safety and efficacy of a particular product, but there is no such omniscience in these matters. In short, for the foreseeable future, surrogate markers are unlikely to replace the need for properly powered and conducted phase III human trials for most second-generation protein products.

Today, for LMWHs, for example, if a product is shown to be safe and effective in thromboprophylaxis for post-operative knee surgery, the innovator company must show that the *identical* product is safe and efficacious for a different indication, such as post-operative hip surgery, via clinical trials. If we subject the same protein product to full trials in the same disease process (*i.e.*, surgical trauma) in minimally different populations (*i.e.*, hip *vs.* knee), there would not appear to be a scientific basis for assuming that such a functionally different second-generation product could forego the same scope of human trials.

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[19] *Id.*

F. Terminology

In its Federal Register notice, FDA asks: (1) 'Please comment on the appropriateness of this notice's working definition of 'follow-on protein' as a protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product,'[20] *and (2) 'Please comment on this notice's working definition of a 'second-generation protein product' as a product similar to an already approved or licensed product but which has been deliberately modified to change one or more of the product's characteristics (e.g., to provide more favorable pharmacokinetic parameters or to decrease immunogenicity).'*[21]

As noted, Pfizer believes that the FDA's proposed distinction between "follow-on proteins" and "second generation protein products" is inappropriate. As discussed throughout these comments, protein products are inherently complex and fragile. As such, they are difficult to copy and characterize by anyone other than the innovator who has intimate knowledge of the manufacturing process. Because second-generation protein products will have different starting material specifications, manufacturing processes, and containers and closures when compared to their innovator predecessors, the final products are likely to differ in some respect. Therefore, it is misleading to suggest that, without extensive clinical study and an exhaustive approval process, "follow-on proteins" can be "a similar version or copy of an already approved or licensed pharmaceutical product."

Moreover, we believe that the distinction between so-called "follow-on proteins" and "second generation protein products" is artificial given the likelihood that the "follow-on proteins" will differ in some respect from their predecessor. Regardless of whether new generations of products have been potentially, unintentionally, or deliberately modified, FDA should regulate them similarly to ensure that only products with proven safety and efficacy reach patients. Accordingly, we believe that all products that fall within FDA's current definitions of "follow-on protein" and "second generation protein product" should be referred to as "second-generation protein products."

In addition, the differences between innovator protein products and second-generation versions should be reflected in both the labeling and in the nonproprietary name (or the United States Adopted Name ("USAN")) chosen for the second-generation product. USANs are well-recognized as providing a vital service to the medical community by providing a means to readily identify identical drug products for substitution and other purposes. Because second-generation versions of protein products cannot be considered identical to the innovator product, a different USAN should be required.

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Pfizer appreciates the opportunity to submit these comments, and would be happy to provide further information regarding any of the issues addressed herein.

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[20] *Id.*

[21] *Id.*